Ceperley
09/368010

```
=> e tacrolimus/cn 5

E1            1     TACRINE HYDROCHLORIDE/CN
E2            1     TACRINE HYDROCHLORIDE MONOHYDRATE/CN
E3            1 --> TACROLIMUS/CN
E4            1     TACROLIMUS HYDRATE/CN
E5            1     TACRYL/CN

=> s e3

L1            1 TACROLIMUS/CN

=> s e4

L2            1 "TACROLIMUS HYDRATE"/CN

=> s l1 or l2

L3            2 L1 OR L2

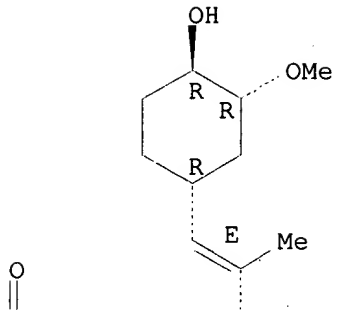
=> d ide can 1-2


L3   ANSWER 1 OF 2  REGISTRY  COPYRIGHT 1999 ACS
RN   109581-93-3  REGISTRY
CN   15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-
     tetrone,
5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-
     dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-
     methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-,
     monohydrate, (3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)- (9CI)  (CA
     INDEX NAME)
OTHER CA INDEX NAMES:
CN   15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-
     tetrone,
5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-
     dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-
     dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-, monohydrate,

[3S-[3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR
     *]]-
OTHER NAMES:
CN   Tacrolimus hydrate
CN   Tsukubaenolide hydrate
FS   STEREOSEARCH
MF   C44 H69 N O12 . H2 O
SR   CA
LC   STN Files:   ADISINSIGHT, AIDSLINE, CA, CANCERLIT, CAPLUS, CHEMCATS, CIN,
       CSCHEM, DRUGPAT, DRUGUPDATES, IPA, MEDLINE, RTECS*, TOXLINE, TOXLIT,
       USAN
         (*File contains numerically searchable property data)
CRN  (104987-11-3)

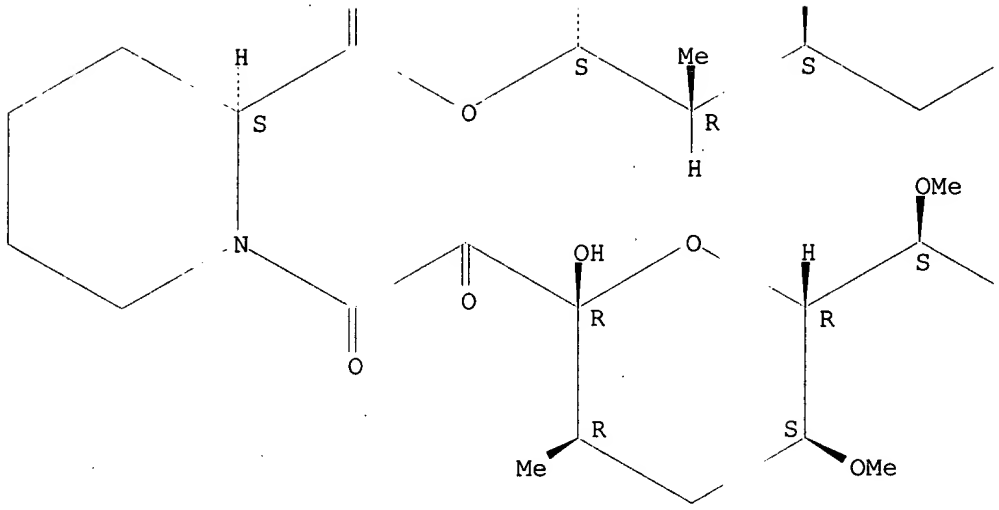
Absolute stereochemistry.
Double bond geometry as described by E or Z.
```

Considered
06/08/00
MTC


OH
OMe
R
R
R
E
Me
O
OH

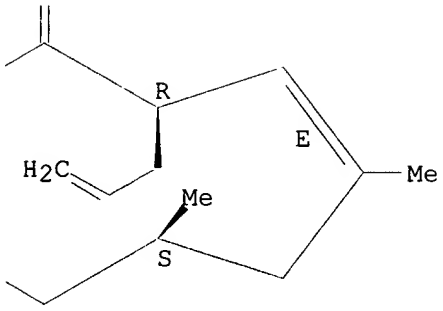

O

PAGE 2-A



• H_2O

PAGE 2-B



5 REFERENCES IN FILE CA (1967 TO DATE)
5 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:262649

REFERENCE 2: 130:332620

REFERENCE 3: 127:185226

REFERENCE 4: 126:181043

REFERENCE 5: 107:175741

L3 ANSWER 2 OF 2 REGISTRY COPYRIGHT 1999 ACS
RN 104987-11-3 REGISTRY
CN 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone,
5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-

methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-, (3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

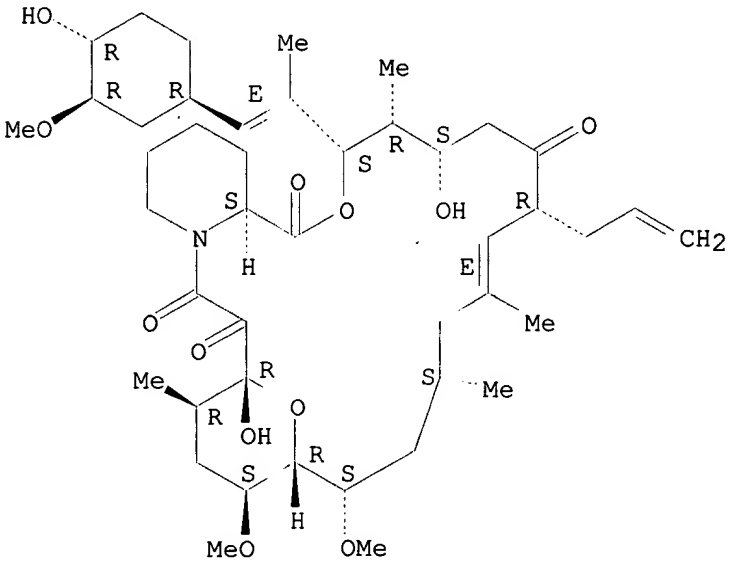
CN 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone,
5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-, [3S-

[3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]-

OTHER NAMES:

CN (-)-FK 506
CN FK 506
CN FR 900506
CN Fujimycin
CN L 679934
CN Prograf
CN **Tacrolimus**
CN Tsukubaenolide
FS STEREOSEARCH
MF C44 H69 N O12
CI COM
SR CA
LC STN Files: ADISINSIGHT, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CIN, DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IFICDB, IFIUDB, MEDLINE, MRCK*, PHAR, PROMT, RTECS*, TOXLINE, TOXLIT, USAN, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO

Absolute stereochemistry.
Double bond geometry as shown.



2532 REFERENCES IN FILE CA (1967 TO DATE)
101 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2539 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:314236

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REFERENCE   2:  131:310475

REFERENCE   3:  131:308489

REFERENCE   4:  131:306682

REFERENCE   5:  131:298638

REFERENCE   6:  131:295287

REFERENCE   7:  131:295276

REFERENCE   8:  131:295138

REFERENCE   9:  131:283459

REFERENCE  10:  131:281563


=> e "fr-900506"/cn 5

E1            1     FR-48736 MONOHYDROCHLORIDE/CN
E2            1     FR-62/CN
E3            0 --> FR-900506/CN
E4            1     FR-A 19/CN
E5            1     FR-B/CN

=> e "fk-506"/cn 5

E1            1     FK-26/CN
E2            1     FK-3000/CN
E3            0 --> FK-506/CN
E4            1     FK-506 BINDING PROTEIN (MOUSE CLONE SAM11 GENE MUFKBP38
REDU
                    CED)/CN
E5            1     FK-506-BINDING PROTEIN (HUMAN FKBP12.6)/CN

=> s fk-506?/cn

L4            2 FK-506?/CN

=> d ide can 1-2


L4   ANSWER 1 OF 2  REGISTRY  COPYRIGHT 1999 ACS
RN   223915-20-6  REGISTRY
CN   Immunophilin (mouse strain C57BL6/DBA2 gene FKBP38 reduced) (9CI)  (CA
     INDEX NAME)
OTHER NAMES:
CN   FK-506 binding protein (mouse clone SAM11 gene muFKBP38 reduced)
CN   FKBP (protein) (mouse strain C57BL6/DBA2 gene FKBP38 reduced)
CN   GenBank AF030635-derived protein GI 2623224
FS   PROTEIN SEQUENCE
MF   Unspecified
CI   MAN
SR   CA
LC   STN Files:   CA, CAPLUS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
               1 REFERENCES IN FILE CA (1967 TO DATE)
```

```
                1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE   1:  130:334369

L4   ANSWER 2 OF 2  REGISTRY  COPYRIGHT 1999 ACS
RN   157858-41-8  REGISTRY
CN   Protein FKBP 12.6 (human FK506-binding reduced) (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   FK-506-binding protein (human FKBP12.6)
FS   PROTEIN SEQUENCE
MF   Unspecified
CI   MAN
SR   CA
LC   STN Files:   CA, CAPLUS, TOXLIT

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
                2 REFERENCES IN FILE CA (1967 TO DATE)
                2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE   1:  123:82999

REFERENCE   2:  121:169804

=> e carboxymethyl oxime/cm 5

'CARBOXYMETHYL OXIME' IS NOT A VALID NUMERIC VALUE
Only valid numeric terms can be EXPANDed in numeric fields.  Valid
numeric terms are zero and any term with an absolute value between 1
E-78 and 1 E74.  Non-numeric characters are not permitted in the
EXPAND command for numeric fields.  To see a list of numeric and text
fields in the current file, enter "HELP SFIELDS" at an arrow
prompt (=>).

=> e carboxymethyl oxime/cn 5

E1            1      CARBOXYMETHYL METHYL CYANOIMIDODITHIOCARBONATE/CN
E2            1      CARBOXYMETHYL NITROCELLULOSE/CN
E3            0 --> CARBOXYMETHYL OXIME/CN
E4            1      CARBOXYMETHYL P-CHLORODITHIOBENZOATE/CN
E5            1      CARBOXYMETHYL PENTAMETHYLENEDITHIOCARBAMATE/CN

=> e keyhole limpet hemocyanin/cn 5

E1            1      KEYFLUOR WHITE RWP/CN
E2            1      KEYFLUOR WHITE ST/CN
E3            0 --> KEYHOLE LIMPET HEMOCYANIN/CN
E4            1      KEYITE/CN
E5            1      KEYKOTE/CN

=> e bovine serum albumin/cn 5

E1            1      BOVINE RIBONUCLEASE A S-PROTEIN/CN
E2            1      BOVINE SEMINAL RNASE (CATTLE ISOENZYME SUBUNIT PRECURSOR
RED
                     UCED)/CN
E3            0 --> BOVINE SERUM ALBUMIN/CN
E4            1      BOVINE SERUM ALBUMIN (330-337)/CN
E5            1      BOVINE SERUM ALBUMIN (503-512)/CN
```

=> s e4-5

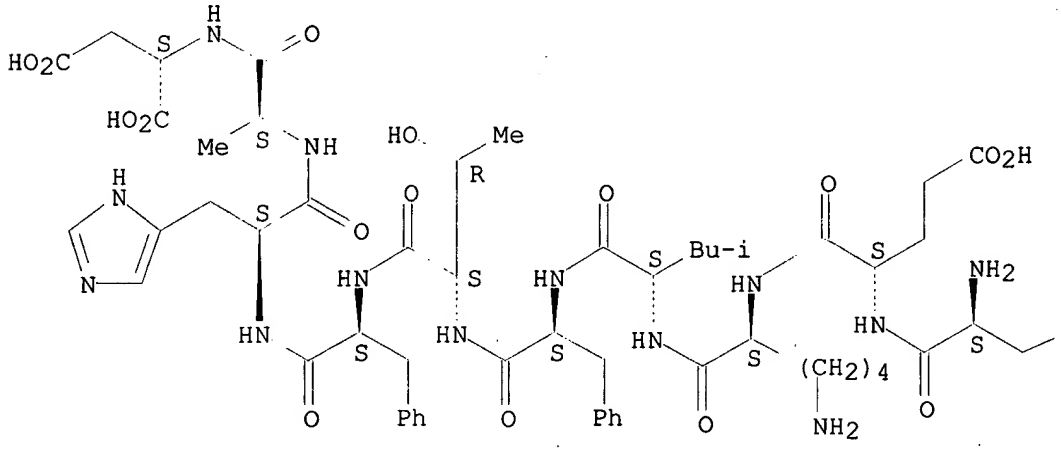
```
             1 "BOVINE SERUM ALBUMIN (330-337)"/CN
             1 "BOVINE SERUM ALBUMIN (503-512)"/CN
L5           2 ("BOVINE SERUM ALBUMIN (330-337)"/CN OR "BOVINE SERUM ALBUMIN
               (503-512)"/CN)
```

=> d 1-2 ide can

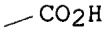
L5 ANSWER 1 OF 2 REGISTRY COPYRIGHT 1999 ACS
RN 91431-86-6 REGISTRY
CN L-Aspartic acid, N-[N-[N-[N-[N-[N-[N-[N2-(N-L-.alpha.-aspartyl-L-.alpha.-glutamyl)-L-lysyl]-L-leucyl]-L-phenylalanyl]-L-threonyl]-L-phenylalanyl]-L-histidyl]-L-alanyl]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **Bovine serum albumin (503-512)**
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C56 H79 N13 O18
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



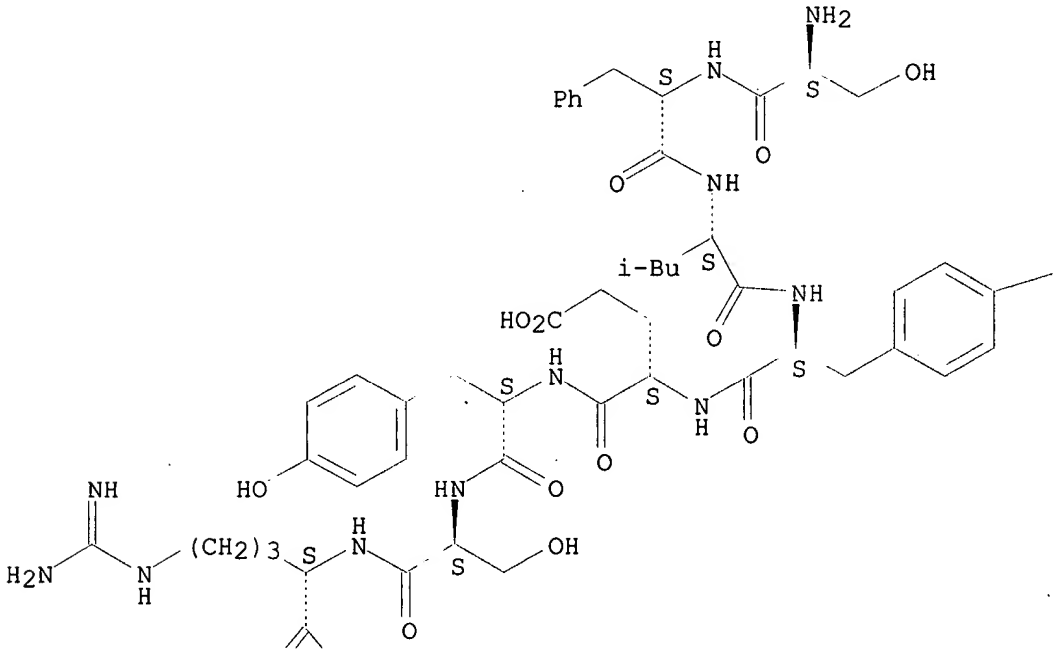
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 101:84125

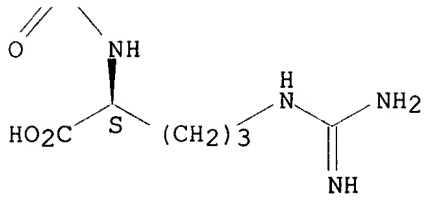
L5 ANSWER 2 OF 2 REGISTRY COPYRIGHT 1999 ACS
RN 91421-93-1 REGISTRY
CN L-Arginine,
L-seryl-L-phenylalanyl-L-leucyl-L-tyrosyl-L-.alpha.-glutamyl-L-tyrosyl-L-seryl-L-arginyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN L-Arginine, N2-[N2-[N-[N-[N-[N-[N-(N-L-seryl-L-phenylalanyl)-L-leucyl]-L-tyrosyl]-L-.alpha.-glutamyl]-L-tyrosyl]-L-seryl]-L-arginyl]-
OTHER NAMES:
CN **Bovine serum albumin (330-337)**
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C56 H81 N15 O16
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.

PAGE 1-A



—OH



3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:135954

REFERENCE 2: 127:221296

REFERENCE 3: 101:84125

=> e ovalbumin/cn 5

E1 1 OVAKO 803/CN
E2 1 OVAKO 837/CN
E3 1 --> OVALBUMIN/CN
E4 1 OVALBUMIN
(11-TYROSINE,13-TYROSINE,16-TYROSINE,29-TYROSINE,5

9-TYROSINE,65-TYROSINE,100-TYROSINE,135-TYROSINE,181-TYROSIN

E,189-TYROSINE,199-TYROSINE,218-TYROSINE,235-TYROSINE,262-TY
ROSINE,307-TYROSINE,/CN
E5 1 OVALBUMIN (CHICKEN CLONE POVCAT-0.900 REDUCED)/CN

=> s e3

L6 1 OVALBUMIN/CN

=> d ide can;e bromacetyl/cn 5

L6 ANSWER 1 OF 1 REGISTRY COPYRIGHT 1999 ACS
RN 9006-59-1 REGISTRY *
* Use of this CAS Registry Number alone as a search term in other STN files
may

```
  result in incomplete search results.  For additional information, enter HELP
  RN* at an online arrow prompt (=>).
CN   Ovalbumin  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Ovalbumins
OTHER NAMES:
CN   Albumins, egg
CN   Allergens, Gal d I
CN   Crystalbumins
CN   Egg albumins
CN   Protalbinic acid
DR   9066-83-5
MF   Unspecified
CI   MAN, CTS
LC   STN Files:   AGRICOLA, AIDSLINE, CA, CANCERLIT, CAPLUS, CHEMCATS,
       CHEMLIST, CIN, CSCHEM, DETHERM*, IPA, MEDLINE, MSDS-OHS, NIOSHTIC,
       RTECS*, TOXLINE, TOXLIT, USPATFULL
         (*File contains numerically searchable property data)
     Other Sources:   DSL**, EINECS**, TSCA**
         (**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
               5 REFERENCES IN FILE CA (1967 TO DATE)
               5 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE   1:  82:110239

REFERENCE   2:  82:58108

REFERENCE   3:  79:38935

REFERENCE   4:  76:150179

REFERENCE   5:  76:82410


E1           1     BROMACETAZOLAMIDE/CN
E2           1     BROMACETOCARBAMIDE/CN
E3           0 --> BROMACETYL/CN
E4           1     BROMACIL/CN
E5           1     BROMACIL MIXTURE WITH CARBARYL/CN

=> e biotin/cn 5

E1           1     BIOTHION/CN
E2           1     BIOTIASTASE 350/CN
E3           1 --> BIOTIN/CN
E4           1     BIOTIN (+)-SULFOXIDE/CN
E5           1     BIOTIN (ACETYL-COA CARBOXYLASE) LIGASE-HOMOLOG (PARACOCCUS
D
                   ENITRIFICANS CLONE PXT-2 GENE BIRA)/CN

=> s e3

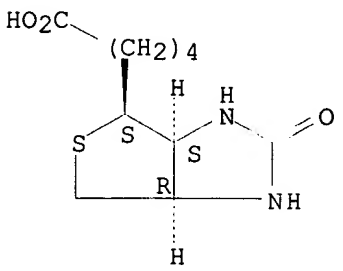
L7           1 BIOTIN/CN

=> d ide can


L7   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 1999 ACS
```

RN 58-85-5 REGISTRY
CN 1H-Thieno[3,4-d]imidazole-4-pentanoic acid, hexahydro-2-oxo-, (3aS,4S,6aR)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Thieno[3,4-d]imidazole-4-pentanoic acid, hexahydro-2-oxo-, [3aS-(3a.alpha.,4.beta.,6a.alpha.)]-
CN **Biotin (8CI)**
OTHER NAMES:
CN (+)-Biotin
CN (+)-cis-Hexahydro-2-oxo-1H-thieno[3,4]imidazole-4-valeric acid
CN Bioepiderm
CN Bios II
CN cis-(+)-Tetrahydro-2-oxothieno[3,4]imidazoline-4-valeric acid
CN Coenzyme R
CN D(+)-Biotin
CN D-Biotin
CN d-Biotin
CN Factor S
CN Factor S (vitamin)
CN Meribin
CN Rovimix H 2
CN Vitamin B7
CN Vitamin H
FS STEREOSEARCH
DR 58073-87-3, 15720-24-8, 22879-79-4, 3672-05-7
MF C10 H16 N2 O3 S
CI COM
LC STN Files: AGRICOLA, AIDSLINE, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS,
CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, HODOC*, HSDB*,
IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PHAR, PIRA, PROMT, RTECS*, SPECINFO, TOXLINE, TOXLIT, USAN, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



6732 REFERENCES IN FILE CA (1967 TO DATE)
1523 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
6761 REFERENCES IN FILE CAPLUS (1967 TO DATE)
8 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 131:314244

REFERENCE 2: 131:308619

REFERENCE 3: 131:308610

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REFERENCE    4:  131:308583

REFERENCE    5:  131:308508

REFERENCE    6:  131:307497

REFERENCE    7:  131:303456

REFERENCE    8:  131:303397

REFERENCE    9:  131:298907

REFERENCE   10:  131:298666


=> e "glucose-6-phosphate dehydrogenase"/cn 5

E1            1     GLUCOSE-6-PHOSPHATE 1-DEHYDROGENASE (THERMOTOGA MARITIMA
GEN
                    E TM1155)/CN
E2            1     GLUCOSE-6-PHOSPHATE 1-DEHYDROGENASE (ZWF) (BORRELIA
BURGDORF
                    ERI STRAIN B31 GENE BB0636)/CN
E3            0 --> GLUCOSE-6-PHOSPHATE DEHYDROGENASE/CN
E4            1     GLUCOSE-6-PHOSPHATE DEHYDROGENASE (ARABIDOPSIS THALIANA
GENE
                     ACG12)/CN
E5            1     GLUCOSE-6-PHOSPHATE DEHYDROGENASE (ARABIDOPSIS THALIANA
GENE
                     ACG9)/CN

=> s glucose-6-phosphate dehydrogenase?/cn

L8           20 GLUCOSE-6-PHOSPHATE DEHYDROGENASE?/CN

=> fil medl,caplus,biosis,embase,wpids;s (l3 or tacrolimus or l4 or fr 900506
or fk 506) and (antibod? or hybridoma or immunogen?)

COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                42.88      43.03

FILE 'MEDLINE' ENTERED AT 13:53:23 ON 02 DEC 1999

FILE 'CAPLUS' ENTERED AT 13:53:23 ON 02 DEC 1999
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L9          480 FILE MEDLINE
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L10 329 FILE CAPLUS
L11 329 FILE BIOSIS
L12 1520 FILE EMBASE
L13 17 FILE WPIDS

TOTAL FOR ALL FILES
L14 2675 (L3 OR TACROLIMUS OR L4 OR FR 900506 OR FK 506) AND (ANTIBOD? OR HYBRIDOMA OR IMMUNOGEN?)

=> s l14 and (carboxymethyl oxime or keyhole limpet hemocyanin or bovine serum albumin or l5 or ovalbumin or l6 or bromoacetyl or biotin or l7 or glucose(3w)phosphate dehydrogenase or l8)

L15 8 FILE MEDLINE
L16 16 FILE CAPLUS
L17 6 FILE BIOSIS
L18 8 FILE EMBASE
L19 1 FILE WPIDS

TOTAL FOR ALL FILES
L20 39 L14 AND (CARBOXYMETHYL OXIME OR KEYHOLE LIMPET HEMOCYANIN OR BOVINE SERUM ALBUMIN OR L5 OR OVALBUMIN OR L6 OR BROMOACETYL OR BIOTIN OR L7 OR GLUCOSE(3W) PHOSPHATE DEHYDROGENASE OR L8)

=> dup rem l20

PROCESSING COMPLETED FOR L20
L21 22 DUP REM L20 (17 DUPLICATES REMOVED)

=> d 1-22 cbib abs

L21 ANSWER 1 OF 22 MEDLINE DUPLICATE 1
1999263903 Document Number: 99263903. Inhibitory effects of FK506 on the development of experimental allergic/immune-mediated blepharoconjunctivitis in Lewis rats by systemic but not by topical administration. Iwamoto H; Yoshida H; Yoshida O; Fukushima A; Ueno H. (Department of Ophthalmology, Kochi Medical School, Nankoku, Japan.)GRAEFES ARCHIVE FOR CLINICAL AND EXPERIMENTAL OPHTHALMOLOGY, (1999 May) 237 (5) 407-14. Journal code: FPR. ISSN: 0721-832X. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.
AB BACKGROUND: FK506 has been used for treatment of cell-mediated immune disorders such as graft rejection in transplantation or Behcet disease. To evaluate the effectiveness of FK506 in another ocular disease model, we injected FK506 in rats with experimental allergic/immune-mediated blepharo conjunctivitis (EAC) the induction mechanism of which depends on cell-mediated immunity. METHODS: Lewis rats were immunized with **ovalbumin** (OVA) in emulsion of complete Freund's adjuvant (CFA). We injected 2 (n = 6), 20 (n = 6) or 200 (n = 5) microg of FK506 intramuscularly daily from the day of immunization (day 0) to day 6. Control rats were not treated with FK506 (n = 4). In addition, we injected 200 microg of FK506 from day 7 to day 13 (n = 12) to compare the timing of FK506 administration (day 0 to day 6, n = 12; control, n = 12). Twenty-one days after immunization, all rats were challenged with OVA by eye drops, and 24 h later they were killed after clinical evaluation and their eyes,

blood and draining lymph nodes were harvested for histology, **antibody** titers and proliferation assay or flow cytometric analysis. In another set of experiments, rats that had received OVA-primed lymph node cells did (n = 9) or did not (n = 9) receive additional FK506 by injection daily for 4 days. Four days after transfer, these rats were challenged with OVA and evaluated as mentioned. To investigate possible suppression of disease by topical administration of FK506, both actively immunized and passively immunized rats received OVA together with 0.3% (weight/volume) of FK506 (n = 16) or vehicle (n = 10) by eye drops and 24 h after challenge, rats were evaluated as mentioned. RESULTS: Development of disease, induced by either active or passive immunization, was inhibited in the group treated with 200 microg of FK506, regardless of timing of administration. Cellular proliferative responses to OVA were inhibited only in this group. Flow cytometry demonstrated a decrease of about 20% in the proportion of all cells made up by CD4-positive T cells. Topical administration of FK506 inhibited the development of EAC, though not significantly. CONCLUSIONS: Systemic treatment with 200 microg of FK506 either in the induction or the effector phase inhibits the development of EAC in Lewis rats. Topical administration is not so effective as systemic administration.

L21 ANSWER 2 OF 22 BIOSIS COPYRIGHT 1999 BIOSIS
1999:153711 Document No.: PREV199900153711. Investigation of autocatalytic folding of peptidyl-prolyl CIS-trans isomerase (FKBP12) from bovine brain with **antibodies** raised to its peptide fragment. Gurvits, B. Ya. (1); Tret'yakov, O. Yu. (1); Galoyan, A. A.. (1) AN Bach Institute Biochemistry, Russian Academy Sciences, 117071 Moscow Russia. Journal of Neurochemistry, (1999) Vol. 72, No. SUPPL., pp. S69. Meeting Info.: 30th Annual Meeting of the American Society for Neurochemistry New Orleans, Louisiana, USA March 14-17, 1999 American Society for Neurochemistry. ISSN: 0022-3042. Language: English.

L21 ANSWER 3 OF 22 CAPLUS COPYRIGHT 1999 ACS
1998:493195 Document No. 129:119871 Fusion proteins with FK506-binding domains as probes in high throughput screening of ligands. Marcy, Alice; Salowe, Scott P.; Wisniewski, Douglas (Merck and Co., Inc., USA). U.S. US 5783398 A 19980721, 16 pp. (English). CODEN: USXXAM. APPLICATION: US 1996-707792 19960904.
AB A high throughput assay for screening for ligands for a protein is described. The protein is prepd. as a fusion protein with an **FK 506**-binding protein (FKBP) that is labeled with [3H]-**FK 506**. The ligand for the second domain of the fusion protein is immobilized, e.g. via a **biotin**/streptavidin pair, to a surface such as the well of a microtiter or microscintillation plate. The effect of potential ligands on the binding of the **FK 506** label to the surface is then assayed. The method is particularly intended for identification of ligands for SH2 domains where it avoids the problems assocd. with rapid turnover and dephosphorylation of the phosphopeptide. The fusion protein can be purified by affinity chromatog. Fusion proteins of FKBP and SH2 domain peptides from ZAP-70, SYK, and LCK proteins are reported.

L21 ANSWER 4 OF 22 CAPLUS COPYRIGHT 1999 ACS
1998:457205 Document No. 129:78842 High throughput ligand assay using fusion proteins based on **FK 506**-binding protein. Salowe,

Scott P. (Merck and Co., Inc., USA). U.S. US 5776696 A 19980707, 14 pp. (English). CODEN: USXXAM. APPLICATION: US 1996-707793 19960904.

AB This invention covers a method of screening for compds. capable of binding to a fusion protein in which the screening system consists of a test compd., a tagged ligand, a fusion protein (target protein, peptide linker and **FK 506**-binding protein), a radiolabeled ligand, and coated scintillation proximity assay (SPA) beads, and then measuring the scintillation counts attributable to the binding of the tagged ligand to the fusion protein in the presence of the test compd. relative to a control assay in the absence of the test compd., so as to det. the effect the test compd. has on the binding of the tagged ligand. This invention provides an immediate means of making use of SPA technol. for the functional assay of ligand binding to a single or multiple signal transduction domains(s), for example a phosphopeptide binding to an SH2 domain. The present invention does not require specialized radiochem. synthesis and is readily adaptable to robotic automation for high capacity screening for agonists, antagonists and/or inhibitors.

L21 ANSWER 5 OF 22 MEDLINE

1999008683 Document Number: 99008683. Effects of FK506 on experimental membranous glomerulonephritis induced by cationized **bovine serum albumin** in rats. Kobayashi M; Muro K; Yoh K; Kondoh M; Iwabuchi S; Hirayama K; Ishizu T; Kikuchi S; Yamaguchi N; Koyama A. (Department of Internal Medicine, Institute of Clinical Medicine, University of Tsukuba, Ibaraki, Japan.)NEPHROLOGY, DIALYSIS, TRANSPLANTATION, (1998 Oct) 13 (10) 2501-8. Journal code: N7J. ISSN: 0931-0509. Pub. country: ENGLAND: United Kingdom. Language: English.

AB BACKGROUND: There have been no reports on the effect of FK5 06, a new immunosuppressive agent, on experimental membranous glomerulonephritis (MN) induced by an exogenous antigen. Therefore we investigated the effects of FK506 on MN induced by cationized **bovine serum albumin** (C-BSA) in rats. METHODS: Two weeks after the rats were immunized with 1 mg of C-BSA and Freund's complete adjuvant, they received intravenous injections of 3 mg/kg of C-BSA 3 times weekly for 4 weeks. Rats were divided into four groups: group A (n = 5) received intramuscular injections of 3 mg/kg of FK506 daily for 5 days beginning 2 days before the first immunization; group B (n =4) received 1 mg/kg of FK506 daily for 2 weeks beginning 2 weeks after the first immunization; and group C (n =4) received 1 mg/kg of FK506 daily for 2 weeks beginning 4 weeks after the first immunization. Group D (n = 5) received no FK506 and served as the control group. Rats were sacrificed 8 weeks after the first immunization. RESULTS: Administration of FK506 in the preimmunization stage almost completely suppressed the development of MN in group A. Histological findings in groups B and C were similar to those in group D, the control group. However, urinary protein excretion was significantly lower in group B (24+/-46 mg/day) and C (220+/-44 mg/day) than in group D (330+/-61 mg/day). Expression of intracellular adhesion molecule-1 in glomeruli and the number of leukocyte functioning-associated molecules-1 were significantly decreased in groups A, B, and C compared with the control group. Administration of FK506 was not associated with any significant side-effects or histological abnormalities. The whole-blood trough levels of FK506 in groups B and C were 9.1 ng/ml and 9.2 ng/ml respectively. CONCLUSIONS: The efficacy of FK506 was significantly increased when the drug was administered in the early phase of immunization in this model. The present study suggests that FK506 may be useful in patients with intractable nephrotic syndrome such as MN.

L21 ANSWER 6 OF 22 CAPLUS COPYRIGHT 1999 ACS
1997:286410 Document No. 126:259161 A high throughput assay for modulators of protein domain interaction using **FK-506**-binding proteins as reporter moieties in fusion proteins. Salowe, Scott P. (Merck and Co., Inc., USA; Salowe, Scott P.). PCT Int. Appl. WO 9710502 A1 19970320, 27 pp. DESIGNATED STATES: W: CA, JP, US; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1996-US14563 19960911. PRIORITY: US 1995-3824 19950915; GB 1996-3486 19960220.

AB A high throughput scintillation proximity assay (SPA) for screening for compds. capable of binding to a fusion protein of a target protein and an FK506-binding protein (FKBP) that avoids the need to prep. labeled ligands for the target protein is described. The assay is particularly intended for screening of ligands modulating the binding of protein kinases to SH domains, esp. SH2 domains. The FKBP fusion protein is labeled with a tritiated **FK-506** deriv. and binding of the fusion protein to the peptide is measured by the radioactivity bound to SPA beads carrying the SH2 domain. The SH2 domain can be immobilized on SPA beads by std. methods such as a **biotin**/streptavidin couple or via an **antibody** conjugate or fusion protein. The prepn. of fusion proteins of the human 12 kilodalton FKBP and Syk kinase, ZAP-70, and p56lck is reported.

L21 ANSWER 7 OF 22 CAPLUS COPYRIGHT 1999 ACS
1997:283821 Document No. 126:261259 Fusion proteins with FK506-binding domains as probes in high throughput screening of ligands. Marcy, Alice; Salowe, Scott P.; Wisniewski, Douglas (Merck and Co., Inc., USA; Marcy, Alice; Salowe, Scott P.; Wisniewski, Douglas). PCT Int. Appl. WO 9710253 A1 19970320, 35 pp. DESIGNATED STATES: W: CA, JP, US; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1996-US14567 19960911. PRIORITY: US 1995-3819 19950915; GB 1996-5210 19960312.

AB A high throughput assay for screening for ligands for a protein is described. The protein is prepd. as a fusion protein with an **FK 506**-binding protein (FKBP) that is labeled with [3H]-**FK 506**. The ligand for the second domain of the fusion protein is immobilized, e.g. via a **biotin**/streptavidin pair, to a surface such as the well of a microtiter or microscintillation plate. The effect of potential ligands on the binding of the **FK 506** label to the surface is then assayed. The method is particularly intended for identification of ligands for SH2 domains where it avoids the problems assocd. with rapid turnover and dephosphorylation of the phosphopeptide. The fusion protein can be purified by affinity chromatog. Fusion proteins of FKBP and SH2 domain peptides are reported.

L21 ANSWER 8 OF 22 CAPLUS COPYRIGHT 1999 ACS
1997:658109 Document No. 127:287961 Inhibitory effects of systemic **FK 506** treatment on allergic blepharoconjunctivitis in rats. Iwamoto, Hiroshi; Yoshida, Osamu; Yoshida, Hironori; Fukushima, Atsuki; Ueno, Hisayuki (Dep. Ophthalmol., Kochi Med. Sch., Nankoku, 783, Japan). Atarashii Ganka, 14(9), 1399-1402 (Japanese) 1997. CODEN: ATGAEX. ISSN: 0910-1810. Publisher: Medikaru Ai Shuppan.

AB We tested the inhibitory effects of **FK 506**, which is known to inhibit cellular immunity in exptl. allergic

blepharoconjunctivitis (EAC) in Lewis rats. We used both active immunization and passive immunization systems. Clin. findings, proliferative responses and **antibody** formation specific for **ovalbumin** (OVA) were evaluated. Clin. findings were inhibited by treatment with **FK 506**. Proliferative responses and **antibody** titer against OVA were also inhibited in the **FK 506**-treated groups. Treatment during early induction phase (day 0-6) was more effective than treatment during late induction phase (day 7-13). These results indicate that systemic **FK 506** treatment inhibits the development of EAC in Lewis rats.

L21 ANSWER 9 OF 22 MEDLINE DUPLICATE 2
1998053140 Document Number: 98053140. Augmentation of natural killer cell activity induced by cytomegalovirus infection in mice treated with FK506. Kageyama S; Matsui S; Hasegawa T; Yoshida Y; Sato H; Yamamura J; Kurokawa M; Yamamoto H; Shiraki K. (Department of Virology, Toyama Medical and Pharmaceutical University, Japan.)ACTA VIROLOGICA, (1997 Aug) 41 (4) 215-20. Journal code: 286. ISSN: 0001-723X. Pub. country: Czech Republic.
Language: English.
AB Comparable rates of patient and graft survival after FK506 and cyclosporine treatments have been reported in the prevention of liver allograft rejection. On this basis, we examined the effect of FK506 on pathogenesis of cytomegalovirus (CMV) infection in mice. FK506 induced apparent immunosuppression in mice which could be monitored by the level of **antibody** production. The effective dose of trinitrophenyl-**keyhole limpet hemocyanin** (TNP-KLH) for 50% reduction in **antibody** production was 0.9 mg/kg. Even in such an immunosuppressed status at this or higher dose of FK506, CMV infection was relatively alleviated, which was observed by the frequency of virus isolation and the mean virus titer of the lungs of mice treated with 0.1-1 mg/kg FK506 in comparison to untreated mice. The dose of FK506 attaining 50% frequency of lung infection was 1.5 mg/kg. The activity of natural killer (NK) cells was enhanced in infected mice. This enhancement was stronger in infected mice treated with FK506 at 0.32 mg/kg and 10 mg/kg than in untreated infected mice on day 3 post infection (p.i.). Thus, an immunosuppressant FK506 augmented inducible NK cell activity and alleviated MCMV infection even under immunosuppression.

L21 ANSWER 10 OF 22 MEDLINE DUPLICATE 3
97165226 Document Number: 97165226. Inhibition by the immunosuppressive agent **FK-506** of antigen-induced airways eosinophilia and bronchial hyperreactivity in mice. Eum S Y; Zuany-Amorim C; Lefort J; Pretolani M; Vargaftig B B. (Unite de Pharmacologie Cellulaire, Institut Pasteur 25, France.)BRITISH JOURNAL OF PHARMACOLOGY, (1997 Jan) 120 (1) 130-6. Journal code: B00. ISSN: 0007-1188. Pub. country: ENGLAND: United Kingdom. Language: English.
AB 1. The effect of the immunosuppressive agent, **FK-506**, an allergen-induced airways eosinophilia and bronchial hyperreactivity (BHR) in hyper IgE mice (BP2 selection) was investigated. 2. Administration of **FK-506** at 2 mg kg-1 s.c., 1 h before and 5 h after the first four **ovalbumin** challenges, reduced the recruitment of eosinophils into the bronchoalveolar lavage fluid (BALF) from 1.36 +/- 0.22 x 10(5) to 0.53 +/- 0.24 x 10(5) cells ml-1 (n = 5-6, P < 0.05; 60% inhibition), inhibited by 80% BHR in response to i.v. 5-HT and practically suppressed BHR in response to inhaled methacholine. 3. The antigen-induced interleukin (IL)-5 formation in the BALF and serum was

inhibited by **FK-506** by 75% in both instances. 4. **FK-506** failed to modify the bronchoconstriction in BP2 mice, suggesting that different mechanisms are involved in acute bronchoconstriction and BHR. 5. The increased number of CD4+, CD8+, CD3+ T lymphocytes in the BALF to antigen-challenged mice was unaffected by **FK-506**. 6. These findings indicate that antigen-induced in vivo IL-5 release and eosinophil, but not T-cell, infiltration into the bronchial lumen of sensitized BP2 mice are targets for the anti-allergic activities of **FK-506**.

L21 ANSWER 11 OF 22 MEDLINE DUPLICATE 4

97431151 Document Number: 97431151. Selective immunomodulatory activity of SK&F 106615, a macrophage-targeting antiarthritic compound, on **antibody** and cellular responses in rats and mice. Badger A M; Newman-Tarr T M; Satterfield J L. (Department of Cellular Biochemistry, SmithKline Beecham Pharmaceuticals, King of Prussia, PA 19406-0939, USA.)IMMUNOPHARMACOLOGY, (1997 Aug) 37 (1) 53-61. Journal code: GY3. ISSN: 0162-3109. Pub. country: Netherlands. Language: English.

AB The azaspiranes are novel immunomodulators which are effective in a variety of animal models of autoimmune disease and transplantation. The compounds appear to target macrophages and alter their functional activity. One of these compounds, SK&F 106615 (N,N-diethyl-8,8-dipropyl-2-azaspiro[4.5]decane-2-propanamine++ + dihydrochloride), is now in phase II clinical trials for rheumatoid arthritis. As many drugs/compounds effective in autoimmune disease and transplantation are overtly immunosuppressive, we designed studies to show that SK&F 106615 has selective immunomodulatory effects and that it does not perform in a manner characteristic of classical immunosuppressive agents on immune function. SK&F 106615 inhibited mouse and rat spleen cell and rat peripheral blood mononuclear cell proliferation in vitro with an IC50 of 500 nM. In vivo, treatment of C57BL/6 mice (15 mg/kg/day, i.p.) or rats (20 mg/kg/day, p.o.) for 2 weeks had no effects on specific **antibody** synthesis to **ovalbumin** (OVA) compared to rapamycin (RAP) which completely suppressed the **antibody** response. Compared to cyclosporin A (CsA), **FK 506** and RAP which suppressed the **antibody** (plaque forming) response to particulate (sheep red blood cells) antigen in a dose responsive manner, SK&F 106615 administered at a dose of 50 mg/kg was inactive. There was an inhibition of the proliferative response of lymph node cells from treated mice and rats to mitogen and antigen in ex vivo assays. SK&F 106615, but not RAP, induced cells in the spleens of mice that could inhibit normal spleen cell proliferation in a co-culture assay. Thus, a selective immunomodulatory effect can be shown for SK&F 106615 in the absence of generalized immunosuppression.

L21 ANSWER 12 OF 22 CAPLUS COPYRIGHT 1999 ACS

1996:483543 Document No. 125:137221 Method of measuring the concentration of FK506-binding protein. Kobayashi, Masakazu; Ohtsuka, Kazuyuki (Fujisawa Pharmaceutical Co., Ltd., Japan). PCT Int. Appl. WO 9618102 A1 19960613, 36 pp. DESIGNATED STATES: W: AU, CA, CN, JP, KR, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1995-JP2427 19951129. PRIORITY: JP 1994-303395 19941207.

AB An enzyme immunoassay method for detecting FK506-binding proteins or measuring the concn. thereof by detecting or quantifying a complex

comprising an FK506-binding protein and the first and second **antibodies** that recognize resp. different antigenic determinants of the protein. The **antibody** may be labeled with **biotin** or alk. phosphatase.

L21 ANSWER 13 OF 22 MEDLINE
96195195 Document Number: 96195195. T cell responses in calcineurin A alpha-deficient mice. Zhang B W; Zimmer G; Chen J; Ladd D; Li E; Alt F W; Wiederrecht G; Cryan J; O'Neill E A; Seidman C E; Abbas A K; Seidman J G. (Howard Hughes Medical Institute, Harvard Medical School, Boston, Massachusetts 02115, USA.)JOURNAL OF EXPERIMENTAL MEDICINE, (1996 Feb 1) 183 (2) 413-20. Journal code: I2V. ISSN: 0022-1007. Pub. country: United States. Language: English.
AB We have created embryonic stem (ES) cells and mice lacking the predominant isoform (alpha) of the calcineurin A subunit (CNA alpha) to study the role of this serine/threonine phosphatase in the immune system. T and B cell maturation appeared to be normal in CNA alpha -/- mice. CNA alpha -/- T cells responded normally to mitogenic stimulation (i.e., PMA plus ionomycin, concanavalin A, and anti-CD3 epsilon **antibody**). However, CNA alpha -/- mice generated defective antigen-specific T cell responses in vivo. Mice produced from CNA alpha -/- ES cells injected into RAG-2-deficient blastocysts had a similar defective T cell response, indicating that CNA alpha is required for T cell function per se, rather than for an activity of other cell types involved in the immune response. CNA alpha -/- T cells remained sensitive to both cyclosporin A and FK506, suggesting that CNA beta or another CNA-like molecule can mediate the action of these immunosuppressive drugs. CNA alpha -/- mice provide an animal model for dissecting the physiologic functions of calcineurin as well as the effects of FK506 and CsA.

L21 ANSWER 14 OF 22 CAPLUS COPYRIGHT 1999 ACS
1995:881452 Document No. 123:296614 Pretargeting methods and compounds with reduced **immunogenicity** of targeting moiety-anti-ligand conjugates or other components employed in diagnostic and therapeutic pretargeting protocols. Graves, Scott S.; Bjorn, Michael J.; Reno, John M.; Axworthy, Donald B.; Fritzberg, Alan R.; Theodore, Louis J. (Neorx Corp., USA). PCT Int. Appl. WO 9515770 A1 19950615, 173 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1994-US14223 19941209. PRIORITY: US 1993-164302 19931209.
AB Methods, compds., compns., and kits that relate to pretargeted delivery of diagnostic and therapeutic agents are disclosed. In particular, methods and agents are provided for reducing the **immunogenicity** of targeting moiety-anti-ligand conjugates or other components employed in diagnostic and therapeutic pretargeting protocols. Prepn. of various conjugates for use in the invention is included. Examples include e.g. in vivo anal. of a radiolabeled chelate-**biotin** conjugate administered after **antibody** pretargeting, clearing agent evaluation, two- and three-step pretargeting methodol., administration of a monoclonal **antibody** (MAb)-streptavidin conjugate in humans, and immunosuppression of MAb-contg. conjugates.

L21 ANSWER 15 OF 22 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
95158362 EMBASE Document No.: 1995158362. Human skin mast cells express functional .beta.1 integrins that mediate adhesion to extracellular matrix

proteins. Columbo M.; Bochner B.S.; Marone G.. Cattedra de Immunologia Clinica, Facolta di Medicina e Chirurgia, Universita de Napoli Frederico II, Via S Pansini 5,80131 Napoli, Italy. Journal of Immunology 154/11 (6058-6064) 1995.
ISSN: 0022-1767. CODEN: JOIMA3. Pub. Country: United States. Language: English. Summary Language: English.

AB We have evaluated the adhesion of human cutaneous mast cells to several components of the extracellular matrix (plasma fibronectin, laminin, collagen type I and IV) and studied whether these cells express the .beta.1 integrins potentially involved in the adhesion to these proteins. Human skin mast cells (5.1 .+-. 1.5% pure) spontaneously adhered to fibronectin and laminin (0.1 to 10 .mu.g/ml) immobilized on plastic surfaces (e.g., 14 .+-. 7.2% and 14 .+-. 4.4% adhesion at 10 .mu.g/ml, respectively). Similar results were obtained with a 90% pure mast cell preparation. In contrast, cutaneous mast cells did not adhere to collagen type I (1.6 .+-. 0.5% adhesion) or type IV (1.2 .+-. 0.8% adhesion). Control adhesion in BSA-coated wells was <5%. Mast cell adhesion to fibronectin was optimal after an incubation period of 60 to 90 min (t(1/2) = 28.2 .+-. 6.2 min), whereas adhesion to laminin was faster (t(1/2) = 10.1 .+-. 1.2 min), being nearly optimal after a 15-min incubation period.

Human skin mast cell adhesion to fibronectin and laminin was found to be dependent on the presence of divalent cations in the extracellular medium.

Dual-color immunofluorescence and flow cytometry were used to evaluate whether human skin mast cells (51.3 .+-. 3.9% pure) express .beta.1 integrins that may mediate cell adhesion to extracellular matrix proteins.

These mast cells were found to express VLA (very late Ag)-3 (75.3 .+-. 35.6 specific fluorescence intensity) and, to lesser degree, VLA-4 and VLA-5 receptors (8.0 .+-. 2.5 and 6.9 .+-. 3.2 specific fluorescence intensity, respectively). In contrast, VLA- 1, VLA-2, and VLA-6 integrins were not expressed significantly. mAb to VLA- 3, VLA-4, and VLA-5 each inhibited by 70% skin mast cell adhesion to fibronectin. mAb to VLA-3 nearly abolished mast cells adhesion to laminin, whereas anti-VLA-4 and anti-VLA-5 were ineffective. Finally, immunosuppressant cyclosporin A (100 nM) and **FK-506** (10 nM) significantly inhibited mast cell adhesion to both fibronectin and laminin ($p < 0.05$). Our data demonstrate that human skin mast cells spontaneously adhere to fibronectin and laminin, and that this adhesion is mediated by VLA-3, VLA-4, and/or VLA-5 integrins on these cells. Interactions between these .beta.1 integrins and extracellular matrix proteins may be involved in perivascular tissue localization of human mast cells in vivo.

L21 ANSWER 16 OF 22 MEDLINE DUPLICATE 5
96087542 Document Number: 96087542. Modulation of the bronchial inflammation in sensitized guinea-pigs by FK506, nedocromil sodium and dexamethasone. Lapa e Silva J R; Ruffie C; Vargaftig B B; Pretolani M. (Hospital Universitario Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Brazil..)EUROPEAN RESPIRATORY JOURNAL, (1995 Aug) 8 (8) 1321-7.
Journal code: ERY. ISSN: 0903-1936. Pub. country: Denmark. Language: English.

AB Guinea-pigs sensitized by a subcutaneous injection of **ovalbumin** in Al(OH)3 and boosted 2 weeks later exhibit marked bronchial hyperresponsiveness to various agonists and intense bronchial wall infiltration by CD4+ T-lymphocytes and eosinophils. We have compared the effect of FK506, a novel immunosuppressive agent, on the mucosal

infiltration by T-cells and eosinophils with the well established drugs, nedocromil sodium and dexamethasone. Sensitized Hartley guinea-pigs were treated subcutaneously for 5 days with FK506 (100 micrograms.kg-1 daily), nedocromil sodium (30 micrograms.kg-1 daily), or dexamethasone (200 micrograms.kg-1 daily). On the day of the experiment, i.e. one week after the booster injection of antigen, the animals were killed, the lungs dissected, frozen and cryostat sections stained by immunohistochemical methods using monoclonal **antibodies** specific for total T-lymphocytes, CD4+ and CD8+ T-cells. Cyanide-resistant eosinophil peroxidase activity was used to stain the eosinophils. Sections were coded and positive cells enumerated in the lamina propria and adventitia of the bronchi. Sensitized and antigen-stimulated vehicle-treated guinea-pigs showed marked infiltration of the bronchial wall by CD4+ T-lymphocytes and eosinophils compared with sensitized, non-antigen stimulated animals. As compared to vehicle, FK506 or dexamethasone abolished the T-cell/eosinophil invasion in the bronchial wall, whereas nedocromil sodium was ineffective in protecting the lungs from T-lymphocyte or eosinophil infiltration. We conclude that both FK506 and dexamethasone are effective in curtailing bronchial inflammation in allergic guinea-pigs, whereas nedocromil sodium did not resolve the inflammation associated with T-lymphocytes or eosinophils.

L21 ANSWER 17 OF 22 CAPLUS COPYRIGHT 1999 ACS

1995:294145 Document No. 122:185334 Homogeneous immunoassays using conjugates of analytes and substituted analogs of **glucose**-6-**phosphate dehydrogenases**. Jakobovits, Edward B.; Silen, Joy L.; Levy, Mark J.; Goodman, Thomas C.; Becker, Martin J.; Ullman, Edwin F.; Caldwell, Robert M.; Bott, Richard R.; Barnett, Christopher Charles (Syntex (U.S.A.) Inc., USA; Genencor International Inc.). PCT Int. Appl. WO 9424559 A2 19941027, 121 pp. DESIGNATED STATES: W: CA, FI, JP; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1994-US3437 19940407. PRIORITY: US 1993-44857 19930408.

AB Immunoassays using mutant forms of **glucose**-6-**phosphate dehydrogenase** (G6PDH) as labels are described. In particular, the assays use conjugates of an analyte or analyte analog and a mutant NAD+-dependent G6PDH. Typically, the mutations involve deletion or substitution of lysine residues or introduction of cysteine residues. The prepn. of such analogs of Leuconostoc G6PDH by site-directed mutagenesis and expression of the cloned genes and the conjugation of analytes to the enzyme analogs are described. Assays for **antibodies** to analytes that measured the inhibition of G6PDH conjugated with the analytes by the **antibodies** are described.

L21 ANSWER 18 OF 22 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.

95082532 EMBASE Document No.: 1995082532. Poster Session 3: Regulation and therapy of **immunogenic** inflammation. Kijlstra A.. Department of Ophthalmo-Immunology, Netherlands Ophthalmic Res. Inst., P.O. Box 12141,1100 AC Amsterdam, Netherlands. Regional Immunology 6/1-2 (151-152) 1994.
ISSN: 0896-0623. CODEN: REGIE3. Pub. Country: United States. Language: English.

L21 ANSWER 19 OF 22 CAPLUS COPYRIGHT 1999 ACS

1994:212008 Document No. 120:212008 Methods and reagents for the determination of immunosuppressive agents and their binding proteins. Lane, Benjamin Clay; Luly, Jay Richard; Smith, Allan H.; Bolling, Timothy J.; Mandecki, Wldozimierz; Pilot-Matias, Tami J. (Abbott Laboratories, USA). PCT Int. Appl. WO 9325533 A1 19931223, 53 pp. DESIGNATED STATES: W: AU, CA, JP, KR; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1993-US5197 19930601. PRIORITY: US 1992-893858 19920605.

AB Assay methods and reagents for detg. the presence or amt. of immunophilin ligands and immunophilins thereof employing a recombinant fusion protein comprising (i) an immunosuppressant binding protein and (ii) a heterologous protein are disclosed. The recombinant fusion protein can also be employed for the evaluation of immunosuppressive activities of immunosuppressive agents in order to det. their efficacy during the course of therapeutic treatment of a patient. Preferably, the recombinant fusion protein comprises a macrolide immunosuppressive agent and CTP:CMP-3-deoxy-D-manno-octulosonate cytidylyl transferase (CKS). When employed in a binding assay format, the recombinant fusion protein provides higher reactivity for the immunophilin ligand under detn. than does the native immunosuppressant binding protein. Also provided are ascomycin (or **FK-506**) and rapamycin analog conjugates with macromols. or detectable moieties. In particular, an immunosuppressant assay reagent comprising recombinantly-prepd. human **FK-506** binding protein (FKBP)-CKS fusion protein immobilized on a solid support material provides a higher signal-to-noise ratio when employed in a competitive heterogeneous assay format than when native FKBP immobilized on a solid support material is employed in such assay format. Ascomycin-C22-carboxymethyloxime-alk. phosphatase conjugate was also prepd. and used as a reagent in assays.

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94004487 Document Number: 94004487. Prolyl isomerases catalyze **antibody** folding in vitro. Lilie H; Lang K; Rudolph R; Buchner J. (Institut fur Biophysik und Physikalische Biochemie, Universitat Regensburg, Germany.)PROTEIN SCIENCE, (1993 Sep) 2 (9) 1490-6. Journal code: BNW. ISSN: 0961-8368. Pub. country: United States. Language: English.

AB Some slow-folding phases in the in vitro refolding of proteins originate from the isomerization of prolyl-peptide bonds, which can be accelerated by a class of enzymes called prolyl isomerases (PPIs). We used the in vitro folding of an **antibody** Fab fragment as a model system to study the effect of PPI on a folding reaction that is only partially reversible. We show here that members of both subclasses of PPIs, cyclophilin and **FK 506** binding protein (FKBP), accelerate the refolding process and increase the yield of correctly folded molecules. An acceleration of folding was not observed in the presence of the specific inhibitor cyclosporin A, but still the yield of correctly folded molecules was increased. **Bovine serum albumin** (BSA) increased the yield comparable to cyclophilin but, in contrast, did not influence the rate of reactivation. These effects were observed only when cyclophilin or BSA were present during the first few seconds of refolding. However, the rate-limiting reactivation reaction is still accelerated when PPI is added several minutes after starting refolding. In contrast, the prokaryotic chaperone GroEL influences the refolding yield when added several minutes after initiating refolding. The results show that PPIs influence the folding of Fab in two different ways.

(1) They act as true catalysts of protein folding by accelerating the rate-limiting isomerization of Xaa-Pro peptide bonds. Proline isomerization is obviously a late folding step and has no influence on the formation of aggregates within the first seconds of the refolding reaction. (ABSTRACT TRUNCATED AT 250 WORDS)

L21 ANSWER 21 OF 22 CAPLUS COPYRIGHT 1999 ACS
1991:647673 Document No. 115:247673 Inhibition of **antibody** production by the immunosuppressive agent, 15-deoxyspergualin. Tepper, M. A.; Petty, B.; Bursuker, I.; Pasternak, R. D.; Cleaveland, J.; Spitalny, G. L.; Schacter, B. (Dep. Immunol., Bristol-Myers Squibb PRI, Wallingford, CT, 06492, USA). Transplant. Proc., 23(1, Bk. 1), 328-31 (English) 1991. CODEN: TRPPA8. ISSN: 0041-1345.

AB 15-Deoxyspergualin (DSC), a deriv. of spergaulin and a metabolite of Bacillus laterosporus, exhibits antitumor and immunosuppressive activity in animal models. Specifically, DSG inhibits **antibody** prodn. and delayed-type hypersensitivity, prolongs allograft rejection, and inhibits the generation of autoimmunity. The mechanism of action of DSG remains unknown, although it is believed to be different from that of cyclosporine A or **FK 506**. In this study, the authors examd. the ability of DSG to suppress a primary and memory **antibody** response in mice immunized with sheep red blood cells or **keyhole limpet hemocyanin**, two highly **immunogenic** antigens.

L21 ANSWER 22 OF 22 CAPLUS COPYRIGHT 1999 ACS DUPLICATE 7
1989:587577 Document No. 111:187577 Preparation of **antibodies** against **FR-900506** and their use in an EIA and kit. Niwa, Mineo; Tamura, Kouichi; Kaizu, Tsutomu; Kobayashi, Masakazu (Fujisawa Pharmaceutical Co., Ltd., Japan). Eur. Pat. Appl. EP 293892 A2 19881207, 17 pp. DESIGNATED STATES: R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE. (English). CODEN: EPXXDW. APPLICATION: EP 1988-108837 19880602. PRIORITY: JP 1987-141776 19870605.

AB Prepn. of polyclonal and monoclonal **antibodies** against the pharmacol. agent **FR-900506** is provided. These anti-**FR-900506 antibodies** are employed in sensitive immobilized-**antibody** EIA methods for detn. of **FR-900506**, e.g. in plasma, by either single or double **antibody** EIA techniques. A kit employing the above **antibodies** for **FR-900506** detn. is provided. Three **hybridomas**, derived from mice immunized against a **bovine serum albumin-FR-900506** conjugate, were produced using std. techniques, and 3 monoclonal **antibodies** were isolated and purified. Each monoclonal **antibody** was sep. adsorbed into wells of an immunoassay plate; wells were washed and nonspecific binding was inhibited. To each well was added peroxidase-labeled **FR-900506** and a std. amt. of dild. **FR-900506**. Following the antigen-**antibody** reaction, peroxidase substrate soln. was added; the enzymic reaction was terminated after 30 min. For each of the monoclonal **antibodies** used, absorbance at 492 nm was inversely related to **FR-900506** concn. in the range 1.0 .times. 10-1-103 ng/mL.

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